## Copy Number Variation (CNV) Classification Scheme

**August 2020**

**Clarity to Better Inform Your Decisions**

### CATEGORY | CRITERIA | WEIGHT
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**A** | CNVs with ≥ 100 genes | 1A
| Well-established microdeletion/duplication syndromes | 1A
| CNV containing a single gene deletion (frameshift, or whole gene) with established clinical validity for autosomal dominant (AD)/X-linked (XL) disease, haploinsufficiency established as mechanism of disease | 1A
| Duplication containing a single gene with established clinical validity for AD/XL disease* and established triplosensitivity (TS); (the TS gene or minimal critical region is fully contained within the observed copy number gain) | 1A

**B** | Deletions with ≥ 35 coding genes | 2B
| Duplications with ≥ 50 coding genes | 2B
| CNV containing a single gene deletion (frameshift, or whole gene) with established clinical validity for AD/XL disease, haploinsufficiency **not** established as mechanism of disease* | 1B
| Described in ≥ 5 probands, internal cases or case reports, with overlapping CNV region and overlapping clinical phenotype | 1B-2B
| Significant disease association in one appropriately sized case-control study. OR>1.5 and p<0.05 when n>1000 case and control chromosomes across studies (Lower CI ≥ 1.5) | 1C-3B
| Good segregation with disease 1B = 5-6 meioses; 2B = >7 meioses | 1B-2B
| Confirmed or assumed de novo alteration | 1C-3B

**C** | Deletions with ≥25-49 total number of unique genes | 1C
| Duplications with ≥35-74 total number of unique genes | 1C
| Moderate segregation with disease (at least 3-4 informative meioses) for rare diseases | 1C
| CNV absent from population databases and internal database, rarity | 1C

**VUS** | Conflicting or insufficient evidence | 

**D** | Large case-control studies show no significant disease association | 1E-1D
| Specific phenotype and lack of co-segregation in family study: Not identified in another affected family member with consistent, specific, well-defined phenotype | 1E-1D
| Specific phenotype and lack of co-segregation in family study: Identified in unaffected family member and specific, well-defined phenotype observed in the proband | 1E-1D

**E** | Described in at least 1 Database of Genomic Variants (DGV) gold standard study OR 2 studies in DGV with frequency 0.5% - 0.99% of the population (n≥100)** | 1E

**F** | Described in at least 1 DGV gold standard study OR 2 studies in DGV with frequency ≥1% of the population (n≥100)** | 1F

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* If partial deletion see pathogenic criterion (PVS1) for predicted loss of function variants

** Does not apply for AR diseases

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